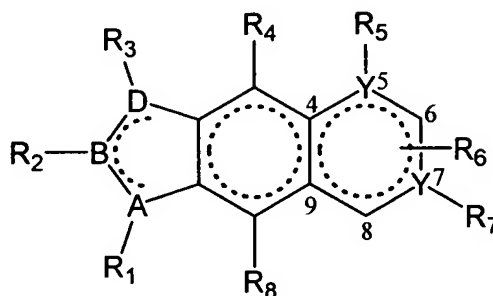


In re Application of: Levitzki et al  
 Serial No.: 10/715,547  
 Filed: November 19, 2003  
 Office Action Mailing Date: January 8, 2008

Examiner: Tamthom N. Truong  
 Group Art Unit: 1624  
 Attorney Docket: 27148

**In the claims:**

1. (Currently Amended) A purified tyrphostin isomer comprising a compound of a general formula:



(Compound II)

wherein,

4, 5, 6, 7, 8 and 9 indicate positions on a terminal 6-member ring;

A, D and Y are each a nitrogen;

B is a carbon;

R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>5</sub> and R<sub>7</sub> are each independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, hydroxy, alkoxy, halo, C-carboxy, O-carboxy, carbonyl, thiocarbonyl, C-amido, guanyl, sulfonyl, trihalomethane-sulfonyl and a pair of electrons, ~~or alternatively, R<sub>1</sub> and R<sub>2</sub> or R<sub>2</sub> and R<sub>3</sub> form a 5-7 member ring structure;~~

R<sub>2</sub> is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, hydroxy, alkoxy, halo, C-carboxy, O-carboxy, carbonyl, thiocarbonyl, C-amido, guanyl, sulfonyl and trihalomethane-sulfonyl, or alternatively, R<sub>1</sub> and R<sub>2</sub> or R<sub>2</sub> and R<sub>3</sub> form a 5-7 member ring structure;

R<sub>6</sub> is selected from the group consisting of alkyl, trihaloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heteroalicyclic, alkoxy, aryloxy, thiohydroxy,

In re Application of: Levitzki et al  
 Serial No.: 10/715,547  
 Filed: November 19, 2003  
 Office Action Mailing Date: January 8, 2008

Examiner: Tamthom N. Truong  
 Group Art Unit: 1624  
 Attorney Docket: 27148

thioalkoxy, thioaryloxy, sulfinyl, sulfonyl, N-sulfonamido, S-sulfonamido, trihalomethylsulfonamido, carbonyl, thiocarbonyl, C-carboxy, O-carboxy, C-amido, N-amido, cyano, nitro, halo, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, ureido, guanyl, guanidino, amino and a physiologically acceptable salt thereof;

R<sub>4</sub> and R<sub>8</sub> are each independently selected from the group consisting of hydrogen, alkyl, trihaloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, thiohydroxy, thioalkoxy, thioaryloxy, sulfinyl, sulfonyl, N-sulfonamido, S-sulfonamido, trihalomethylsulfonamido, carbonyl, thiocarbonyl, C-carboxy, O-carboxy, C-amido, N-amido, cyano, nitro, halo, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, ureido, guanyl, guanidino, amino and -NR<sub>10</sub>R<sub>11</sub> and, a physiologically acceptable salt thereof;

R<sub>10</sub> and R<sub>11</sub> are each independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, carbonyl and sulfonyl, or alternatively R<sub>10</sub> and R<sub>11</sub> form a five- or six-member heteroalicyclic ring; and, a physiologically acceptable salt thereof;

whereas R<sub>6</sub> is at position 6.

2. (Previously Presented) The purified tyrphostin isomer of claim 1, wherein

R<sub>1</sub> and R<sub>2</sub> are each independently selected from the group consisting of alkyl, alkoxy, halogen, nitro and amine group;

R<sub>3</sub>, R<sub>5</sub> and R<sub>7</sub> are each a pair of electrons;

R<sub>6</sub> is an aryl, selected from the group consisting of phenyl, ferrocene, thiophene, furane, pyrrole, indole, thiazole, imidazole and pyridine.

In re Application of: Levitzki et al  
Serial No.: 10/715,547  
Filed: November 19, 2003  
Office Action Mailing Date: January 8, 2008

Examiner: Tamthom N. Truong  
Group Art Unit: 1624  
Attorney Docket: 27148

3. (Previously Presented) The purified tyrphostin isomer of claim 2, wherein

R<sub>1</sub> and R<sub>2</sub> are each a methyl;

R<sub>4</sub> and R<sub>8</sub> are each a hydrogen.

4. (Withdrawn) The preparation of claim 1, wherein said preparation is enriched for Compound I in which R<sub>6</sub> is at position 6.

5. (Withdrawn) The preparation of claim 1, wherein said preparation is enriched for Compound I in which R<sub>6</sub> is at position 7.

6-8. (Canceled)

9. (Previously Presented) A pharmaceutical composition comprising, as an active ingredient, the purified tyrphostin isomer of claim 1 and a pharmaceutically acceptable carrier.

10. (Original) The pharmaceutical composition of claim 9, wherein said pharmaceutically acceptable carrier is a slow release carrier.

11. (Original) The pharmaceutical composition of claim 10, wherein said slow release carrier is polylactic acid.

12. (Withdrawn) A method of treating or preventing a protein tyrosine kinase related disorder in an organism, the method comprising the step of administering to said organism a therapeutically effective amount of the pharmaceutical composition of claim 9.

In re Application of: Levitzki et al  
Serial No.: 10/715,547  
Filed: November 19, 2003  
Office Action Mailing Date: January 8, 2008

Examiner: Tamthom N. Truong  
Group Art Unit: 1624  
Attorney Docket: 27148

13. (Withdrawn) The method of claim 12, wherein said protein tyrosine kinase related disorder is selected from the group consisting of an EGF related disorder, a PDGF related disorder, an IGF related disorder and a met related disorder.

14. (Withdrawn) The method of claim 12, wherein said protein tyrosine kinase related disorder is selected from the group consisting of a cell proliferative disorder, a fibrotic disorder and a metabolic disorder.

15. (Withdrawn) The method of claim 14, wherein said cell proliferative disorder is selected from the group consisting of papilloma, blastoglioma, Kaposi's sarcoma, melanoma, lung cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, astrocytoma, head cancer, neck cancer, bladder cancer, breast cancer, lung cancer, colorectal cancer, thyroid cancer, pancreatic cancer, gastric cancer, hepatocellular carcinoma, leukemia, lymphoma, Hodgkin's disease, Burkitt's disease, arthritis, rheumatoid arthritis, diabetic retinopathy, angiogenesis, restenosis, in-stent restenosis, vascular graft restenosis.

16. (Withdrawn) The method of claim 14, wherein said cell fibrotic disorder is selected from the group consisting of pulmonary fibrosis, hepatic cirrhosis, atherosclerosis, glomerulonephritis, diabetic nephropathy, thrombic microangiopathy syndromes, transplant rejection.

17. (Withdrawn) The method of claim 14, wherein said cell metabolic disorder is selected from the group consisting of psoriasis, diabetes, wound healing, inflammation, and neurodegenerative diseases.

18. (Withdrawn) The method of claim 12, wherein said protein tyrosine kinase related disorder is selected from the group consisting of papilloma, blastoglioma, Kaposi's sarcoma, melanoma, lung cancer, ovarian cancer, prostate

In re Application of: Levitzki et al  
Serial No.: 10/715,547  
Filed: November 19, 2003  
Office Action Mailing Date: January 8, 2008

Examiner: Tamthom N. Truong  
Group Art Unit: 1624  
Attorney Docket: 27148

cancer, squamous cell carcinoma, astrocytoma, head cancer, neck cancer, bladder cancer, breast cancer, small-cell lung cancer, colorectal cancer, thyroid cancer, pancreatic cancer, gastric cancer, hepatocellular carcinoma, leukemia, lymphoma, Hodgkin's disease, Burkitt's disease, psoriasis, pulmonary fibrosis, arthritis, rheumatoid arthritis, diabetic retinopathy, restenosis, in-stent restenosis, vascular graft restenosis, hepatic cirrhosis, atherosclerosis, angiogenesis, glomerulonephritis, diabetic nephropathy, thrombic microangiopathy syndromes, transplant rejection, autoimmune disease, wound healing, inflammation, neurodegenerative diseases, diabetes and hyperimmune disorders.

19. (Withdrawn) The method of claim 12, wherein said organism is a mammal.

20. (Withdrawn) The method of claim 19, wherein said mammal is a human.

21. (Withdrawn) A method of locally treating or preventing a disorder of a tissue of an organism comprising the step of locally applying the pharmaceutical composition of claim 9 onto said tissue.

22. (Withdrawn) The method of claim 21, wherein said organism is a human.

23. (Withdrawn) The method of claim 21, wherein said tissue is selected from the group consisting of blood vessel, lung and skin.

24. (Withdrawn) A method of inhibiting cell proliferation comprising the step of subjecting the cells to the tyrphostin preparation of claim 1.

In re Application of: Levitzki et al  
 Serial No.: 10/715,547  
 Filed: November 19, 2003  
 Office Action Mailing Date: January 8, 2008

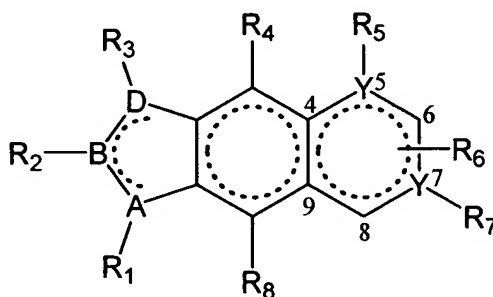
Examiner: Tamthom N. Truong  
 Group Art Unit: 1624  
 Attorney Docket: 27148

25. (Withdrawn) The method of claim 24, wherein said cells are of an organism, whereas subjecting the cells to said preparation is effected *in vivo*.

26. (Withdrawn) The method of claim 25, wherein said organism is a human.

27. (Withdrawn) The method of claim 24, wherein subjecting the cells to said preparation is effected *in vitro*.

28. (Currently Amended) A method of enriching, for a specific isomer, a tyrphostin of a general formula:



(Compound II)

wherein,

4, 5, 6, 7, 8 and 9 indicate positions on a terminal 6-member ring;

A, D and Y are each a nitrogen;

B is a carbon;

R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>5</sub> and R<sub>7</sub> are each independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, hydroxy, alkoxy, halo, C-carboxy, O-carboxy, carbonyl, thiocarbonyl, C-amido, guanyl, sulfonyl, trihalomethane-sulfonyl and a pair of electrons, or alternatively, R<sub>1</sub> and R<sub>2</sub> or R<sub>2</sub> and R<sub>3</sub> form a 5-7 member ring structure;

In re Application of: Levitzki et al  
 Serial No.: 10/715,547  
 Filed: November 19, 2003  
 Office Action Mailing Date: January 8, 2008

Examiner: Tamthom N. Truong  
 Group Art Unit: 1624  
 Attorney Docket: 27148

R<sub>2</sub> is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, hydroxy, alkoxy, halo, C-carboxy, O-carboxy, carbonyl, thiocarbonyl, C-amido, guanyl, sulfonyl and trihalomethane-sulfonyl, or alternatively, R<sub>1</sub> and R<sub>2</sub> or R<sub>2</sub> and R<sub>3</sub> form a 5-7 member ring structure;

R<sub>6</sub> is selected from the group consisting of alkyl, trihaloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, thiohydroxy, thioalkoxy, thioaryloxy, sulfinyl, sulfonyl, N-sulfonamido, S-sulfonamido, trihalomethylsulfonamido, carbonyl, thiocarbonyl, C-carboxy, O-carboxy, C-amido, N-amido, cyano, nitro, halo, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, ureido, guanyl, guanidino, amino and a physiologically acceptable salt thereof;

R<sub>4</sub> and R<sub>8</sub> are each independently selected from the group consisting of hydrogen, alkyl, trihaloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, thiohydroxy, thioalkoxy, thioaryloxy, sulfinyl, sulfonyl, N-sulfonamido, S-sulfonamido, trihalomethylsulfonamido, carbonyl, thiocarbonyl, C-carboxy, O-carboxy, C-amido, N-amido, cyano, nitro, halo, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, ureido, guanyl, guanidino, amino and -NR<sub>10</sub>R<sub>11</sub> and, a physiologically acceptable salt thereof;

R<sub>10</sub> and R<sub>11</sub> are each independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, carbonyl and sulfonyl, or alternatively R<sub>10</sub> and R<sub>11</sub> form a five- or six-member heteroalicyclic ring; and, a physiologically acceptable salt thereof;

whereas, for each molecule R<sub>6</sub> is at position 6 or 8;

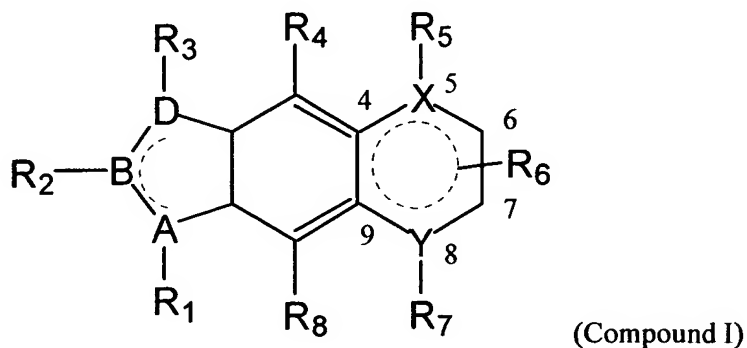
the method comprising the steps of:

- (a) chromatographing a preparation of the tyrphostin through a matrix, thereby separating isomers in said preparation;
- (b) collecting at least one specific isomer.

In re Application of: Levitzki et al  
 Serial No.: 10/715,547  
 Filed: November 19, 2003  
 Office Action Mailing Date: January 8, 2008

Examiner: Tamthom N. Truong  
 Group Art Unit: 1624  
 Attorney Docket: 27148

29. (Original) The method of claim 28, further comprising the step of:  
 (c) crystallizing said at least one specific isomer.
30. (Previously Presented) The method of claim 28, wherein  
 $R_1$  and  $R_2$  are each independently selected from the group consisting of alkyl, alkoxy, halogen, nitro and amine group;  
 $R_3$ ,  $R_5$  and  $R_7$  are each a pair of electrons;  
 $R_6$  is an aryl, selected from the group consisting of phenyl, ferrocene, thiophene, furane, pyrrole, indole, thiazole, imidazole and pyridine.
31. (Original) The method of claim 30, wherein  
 $R_1$  and  $R_2$  are each a methyl;  
 $R_4$  and  $R_8$  are each a hydrogen.
32. (Withdrawn) A method for preparing a pharmaceutical composition for slow release of a tyrphostin comprising the steps of:  
 (a) providing an isomer-enriched tyrphostin preparation comprising a compound of a general formula:

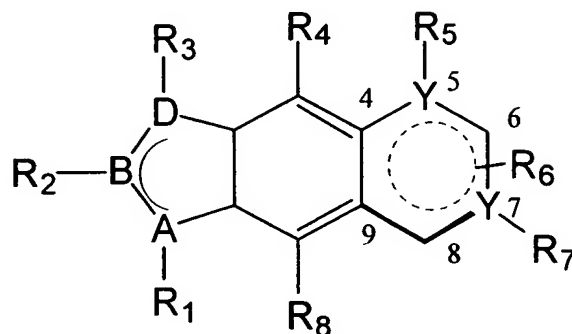


or



In re Application of: Levitzki et al  
 Serial No.: 10/715,547  
 Filed: November 19, 2003  
 Office Action Mailing Date: January 8, 2008

Examiner: Tamthom N. Truong  
 Group Art Unit: 1624  
 Attorney Docket: 27148



(Compound II)

wherein,

4, 5, 6, 7, 8 and 9 indicate positions on a terminal 6-member ring;

A, B, D, X and Y are each independently selected from the group consisting of carbon, nitrogen, oxygen and sulfur;

R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>5</sub> and R<sub>7</sub> are each independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, hydroxy, alkoxy, halo, C-carboxy, O-carboxy, carbonyl, thiocarbonyl, C-amido, guanly, sulfonyl, trihalomethane-sulfonyl and a pair of electrons, or alternatively, R<sub>1</sub> and R<sub>2</sub> or R<sub>2</sub> and R<sub>3</sub> form a 5-7 member ring structure;

R<sub>6</sub> is selected from the group consisting of alkyl, trihaloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, thiohydroxy, thioalkoxy, thioaryloxy, sulfinyl, sulfonyl, N-sulfonamido, S-sulfonamido, trihalomethylsulfonamido, carbonyl, thiocarbonyl, C-carboxy, O-carboxy, C-amido, N-amido, cyano, nitro, halo, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, ureido, guanly, guanidino, amino and a physiologically acceptable salt or a prodrug thereof;

R<sub>4</sub> and R<sub>8</sub> are each independently selected from the group consisting of hydrogen, alkyl, trihaloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, thiohydroxy, thioalkoxy, thioaryloxy, sulfinyl, sulfonyl, N-sulfonamido, S-sulfonamido, trihalomethylsulfonamido,

In re Application of: Levitzki et al  
 Serial No.: 10/715,547  
 Filed: November 19, 2003  
 Office Action Mailing Date: January 8, 2008

Examiner: Tamthom N. Truong  
 Group Art Unit: 1624  
 Attorney Docket: 27148

carbonyl, thiocarbonyl, C-carboxy, O-carboxy, C-amido, N-amido, cyano, nitro, halo, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, ureido, guanyl, guanidino, amino and  $-NR_{10}R_{11}$  and, a physiologically acceptable salt or a prodrug thereof;

$R_{10}$  and  $R_{11}$  are each independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, carbonyl and sulfonyl, or alternatively  $R_{10}$  and  $R_{11}$  form a five- or six-member heteroalicyclic ring; and, a physiologically acceptable salt or a prodrug thereof;

whereas, for Compound I, said preparation is enriched either for  $R_6$  at position 6 or for  $R_6$  at position 7, or, for Compound II, said preparation is enriched either for  $R_6$  at position 6 or for  $R_6$  at position 8;

(b) dissolving or dispersing a slow release carrier and said isomer-enriched tyrphostin preparation in an organic solvent for obtaining an organic solution containing said carrier and said isomer-enriched tyrphostin preparation;

(c) adding said organic solution into an aqueous solution for obtaining an oil-in-water-type emulsion; and

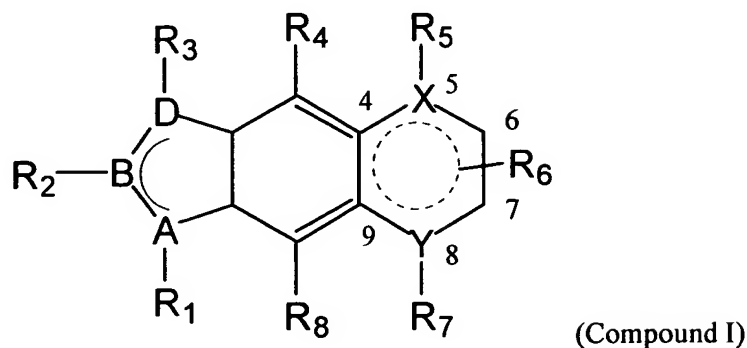
(d) evaporating said organic solvent from said oil-in-water-type emulsion for obtaining a colloidal suspension of particles containing said slow release carrier and said isomer-enriched tyrphostin preparation.

33. (Withdrawn) The method of claim 32, wherein said slow release carrier is polylactic acid.

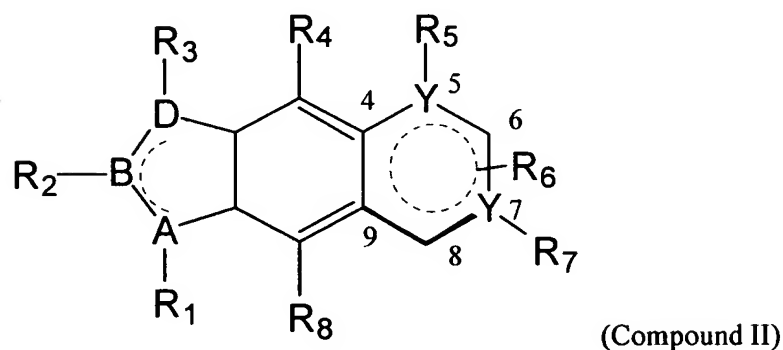
34. (Withdrawn) A stent comprising a substantially tubular body, the body is made of a material designed for slow release of a tyrphostin preparation, said tyrphostin preparation including a compound of a general formula:

In re Application of: Levitzki et al  
 Serial No.: 10/715,547  
 Filed: November 19, 2003  
 Office Action Mailing Date: January 8, 2008

Examiner: Tamthom N. Truong  
 Group Art Unit: 1624  
 Attorney Docket: 27148



or



wherein,

4, 5, 6, 7, 8 and 9 indicate positions on a terminal 6-member ring;

A, B, D, X and Y are each independently selected from the group consisting of carbon, nitrogen, oxygen and sulfur;

R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>5</sub> and R<sub>7</sub> are each independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, hydroxy, alkoxy, halo, C-carboxy, O-carboxy, carbonyl, thiocarbonyl, C-amido, guanly, sulfonyl, trihalomethane-sulfonyl and a pair of electrons, or alternatively, R<sub>1</sub> and R<sub>2</sub> or R<sub>2</sub> and R<sub>3</sub> form a 5-7 member ring structure;

R<sub>6</sub> is selected from the group consisting of alkyl, trihaloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy,

In re Application of: Levitzki et al  
Serial No.: 10/715,547  
Filed: November 19, 2003  
Office Action Mailing Date: January 8, 2008

Examiner: Tamthom N. Truong  
Group Art Unit: 1624  
Attorney Docket: 27148

thiohydroxy, thioalkoxy, thioaryloxy, sulfinyl, sulfonyl, N-sulfonamido, S-sulfonamido, trihalomethylsulfonamido, carbonyl, thiocarbonyl, C-carboxy, O-carboxy, C-amido, N-amido, cyano, nitro, halo, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, ureido, guanyl, guanidino, amino and a physiologically acceptable salt or a prodrug thereof;

R<sub>4</sub> and R<sub>8</sub> are each independently selected from the group consisting of hydrogen, alkyl, trihaloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, thiohydroxy, thioalkoxy, thioaryloxy, sulfinyl, sulfonyl, N-sulfonamido, S-sulfonamido, trihalomethylsulfonamido, carbonyl, thiocarbonyl, C-carboxy, O-carboxy, C-amido, N-amido, cyano, nitro, halo, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, ureido, guanyl, guanidino, amino and -NR<sub>10</sub>R<sub>11</sub> and, a physiologically acceptable salt or a prodrug thereof;

R<sub>10</sub> and R<sub>11</sub> are each independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, carbonyl and sulfonyl, or alternatively R<sub>10</sub> and R<sub>11</sub> form a five- or six-member heteroalicyclic ring; and, a physiologically acceptable salt or a prodrug thereof;

whereas, for Compound I, said preparation is enriched either for R<sub>6</sub> at position 6 or for R<sub>6</sub> at position 7, or, for Compound II, said preparation is enriched either for R<sub>6</sub> at position 6 or for R<sub>6</sub> at position 8.